SFDA SAFETY SIGNAL

"A signal is defined by the SFDA as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature"

18-10-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Atezolizumab and the Risk of Pericardial Effusion

The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of ***Pericardial Effusion*** *associated with the use of* ***Atezolizumab****. The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Atezolizumab is a programmed cell death ligand 1 (PD-L1) blocking antibody indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma. PD-L1 may be expressed on tumor cells and/or tumor infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production [1]. Pericardial effusion is the presence of an abnormal amount of fluid and/or an abnormal character to fluid in the pericardial space. It can be caused by a variety of local and systemic disorders, or it may be idiopathic. Signs and symptoms of pericardial effusion include the following: chest pain, pressure, light-headedness, syncope, palpitations, cough, dyspnea, hoarseness, anxiety, confusion and hiccoughs [2]. The aim of this review is to evaluate the risk of Pericardial Effusion associated with the use of Atezolizumab and to suggest regulatory recommendations if required.

Methodology

Signal Detection team at the National Pharmacovigilance Center (NPC) of Saudi Food and Drug Authority (SFDA) performed a comprehensive signal review using its national database as well as the World Health Organization (WHO) database (VigiBase), to retrieve related information for assessing the causality between Atezolizumab and the risk of Pericardial Effusion [3]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [4].

Results

Case Review: As of August, 2021, there were 38 global Individual case safety reports (ICSRs) for the combined drug/adverse drug reaction [3]. All reported cases were evaluated for causality by the reviewers. Four of the assessable ICSRs were supportive of association, with two being probable and two being possible. Furthermore, positive dechallenge was reported in two cases. [4].

Data Mining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association. The results of (IC= 2.9) revealed a positive statistical association for the drug/ADR combination, meaning "Pericardial Effusion" with the use of "Atezolizumab" has been observed more than expected compared to other medications available in WHO database [3].

Literature

A pharmacovigilance review of Eudravigilance, database to manage the collection and analysis of suspected adverse reactions to medicines authorised in the European Economic Area, was conducted to examine risk of cardiotoxicity with PD-1 and PD-L1 inhibitors. Reviewers identified Pericardial Effusion as the most reported cardiac event associated with these drugs [5]. Furthermore, a 69-year-old man with a stage 4 non-small cell lung cancer (NSCLC) had been included in the experimental arm of an open label, phase 3, randomized clinical trial evaluating the efficacy of Atezolizumab in combination with cabozantinib in metastatic NSCLC progressing after chemotherapy. The patient had already received five intravenous infusions of Atezolizumab (1200mg every 3 weeks) when he was admitted to the hospital. On admission, a low voltage was seen on the electrocardiogram. The clinical assessment was completed by a transthoracic echocardiogram (TTE) showing a cardiac tamponade due to a major pericardial effusion. After that, treatment was stopped, and third line chemotherapy was eventually initiated [6].

Conclusion

The weighted cumulative evidence identified from the reported cases, data mining, and literature are sufficient to support a causal association between Atezolizumab and the risk of Pericardial Effusion. Health regulators and health care professionals must be aware of this potential risk and it is advisable to monitor any signs or symptoms in treated patients.

Report Adverse Drug Events (ADRs) to the SFDA

The SFDA urges both healthcare professionals and patients to continue reporting adverse drug reactions (ADRs) resulted from using any medications to the SFDA either online, by regular mail or by fax, using the following contact information:

National Pharmacovigilance Center (NPC)
Saudi Food and Drug Authority-Drug sector
4904 northern ring branch rd
Hittin District
Riyadh 13513 – 7148
Kingdom of Saudi Arabia
Toll free number: 19999
Email: NPC.Drug@sfda.gov.sa

References:

1. Hoffmann-La Roche Ltd (2020). Saudi Summary of Product Characteristics (SPC) of Tecentriq- Atezolizumab Available at: https: //sdi.sfda.gov.sa
2. Emedicine.medscape.com. 2021. Pericardial Effusion: Practice Essentials, Background, Pathophysiology. [online] Available at: https://emedicine.medscape.com/article/157325-overview
3. Vigilyze.who-umc.org. 2021. [online] Available at: <https://vigilyze.who-umc.org/>
4. Uppsala Monitoring Center (UMC) (2021), The use of the WHO-UMC system for standardized case causality assessment; Available at https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf?ua=1
5. Mascolo, A., Scavone, C., Ferrajolo, C., Rafaniello, C., Danesi, R., Del Re, M., Russo, A., Coscioni, E., Rossi, F., Alfano, R., & Capuano, A. (2021). Immune Checkpoint Inhibitors and Cardiotoxicity: An Analysis of Spontaneous Reports in Eudravigilance. Drug safety, 44(9), 957–971. https://doi.org/10.1007/s40264-021-01086-8
6. Benjamin, L., Jean-Charles, G., Laurence, M., Adrien, R., Terry, L., & Régis, D. (2021). Malignant pericardial effusion complicated by cardiac tamponade under atezolizumab. SAGE open medical case reports, 9, 2050313X211036005. https://doi.org/10.1177/2050313X211036005